MICROCHIP AND WEDGE ION FUNNELS AND PLANAR ION BEAM ANALYZERS USING SAME

FEDERALLY-SPONSORED RESEARCH AND DEVELOPMENT

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FIELD OF THE INVENTION

The invention relates to systems and methods for guidance and focusing of ions, particularly in the context of mass spectrometry (MS) and ion mobility spectrometry (IMS). Specifically, the invention discloses an electrodynamic ion funnel of new design and construction technology, and novel MS and IMS operational modes that it enables.

BACKGROUND OF THE INVENTION

Modern biomedical and environmental research and applications depend on detailed and comprehensive characterization of complex samples. The demands of specificity, sensitivity, and speed have made mass spectrometry (MS) the prevailing platform for such analyses. Most real samples are sufficiently challenging to necessitate one or more separation steps prior to MS. These separations are typically performed in the condensed phase, using liquid chromatography (LC) or capillary electrophoresis (CE). Nowadays, those methods are increasingly replaced or supplemented by separations in gases relying on ion mobility spectrometry (IMS), including field asymmetric waveform IMS (FANS).

MS can analyze ions only. For large and fragile molecules including proteins, peptides, DNA strands of significant length, and most metabolites and other biomolecules, electrospray ionization (ESI) and its derivatives such as desorption ESI or laser ablation ESI are commonly employed. The ESI efficiency is maximized at high (near-atmospheric) gas pressure and drops with decreasing pressure to zero in vacuum, hence ESI sources are normally operated at ambient pressure. Some ion sources, for example matrix-assisted laser desorption ionization (MALDI), can perform in vacuum, but are often employed at ambient pressure for speed and convenience. Use of such atmospheric pressure ionization (API) sources inevitably creates the problem of effective ion transfer into the MS vacuum through a necessarily narrow orifice that is typically much smaller than the produced ion swarm. The same issue arises when coupling IMS or FAIMS stages among themselves or to MS, where ion beams or packets that spread (because of diffusion and Coulomb repulsion) during separation must be introduced into an MS or another IMS stage via a narrow aperture.

In API/MS systems, the MS inlet has typically been fashioned as a curtain plate/orifice assembly (FIG. **1***a*) or a heated capillary (FIG. **1***b*). These differ in how the solvated ions generated by ESI are desolvated: by gas counter-flow while being pushed forward by an electric field (FIG. **1***a*) or heated gas flow (FIG. **1***b*). In either case, the conductance limit between the atmosphere and MS vacuum is much narrower than the incoming ion plume, leading to major ion losses even with a single ESI emitter. Losses are larger yet with emitter arrays that provide more effective and uniform ionization at lower liquid flow per emitter, but deliver ions over a wider area (FIG. **1***c*). The typical pressure in the first MS chamber after either interface is several Torr, the maximum for effective evacuation by standard vacuum pumps. Thus the gas coming from atmosphere supersonically expands, greatly broadening the ion beams beyond the aperture of the skimmer leading to the next MS chamber, which causes further losses. Thus ~1% and often much less of ions produced by ESI are transmitted to the high-vacuum MS regions, limiting the MS sensitivity and dynamic range. Similarly, in drift-tube (DT) IMS, ion packets expand orthogonally to the tube axis during separation, and <1% of ions enter the following MS stage via a pinhole at the tube terminus (FIG. **1***d*). In conjunction with losses at the tube front and low DTIMS duty cycle, that has reduced sensitivity so severely as to preclude commercialization of DTIMS/MS systems and their use in most practical analyses. For FAIMS devices, the analytical gap geometry is crucial, Units with curved gaps feature an inhomogeneous electric field that focuses ions to the median. With hemispherical caps, those units produce tight beams that can pass through narrow MS inlets with few losses. This focusing also constrains the FANS resolving power, obstructing many applications. Planar FAIMS units have a homogeneous field that effects no focusing and thus may provide exceptional resolution, but ions freely diffuse, broadening the beam in the plane of the gap cross-section. In transverse-cylindrical FAILS units, ions are focused to the gap median but also freely diffuse in the lateral direction. Extracting such broadened beams through standard inlets to an MS (or reduced-pressure IMS) stage is associated with huge ion losses that limit the utility of high-resolution FAILS (FIG. **1***e*). Slit-aperture MS inlets that better match the rectangular cross-section of ion beams exiting planar FAIMS devices provide some improvement, but large losses remain.

The need to focus ion beams or packets at substantial gas pressure for transmission into lower-pressure instrument stages through a necessarily tight aperture is broadly encountered in MS and hyphenated MS, and is often critical for successful analyses. This need has previously been addressed using electrodynamic ion funnels, at the simplest comprising stacks of electrodes separated by insulator gaps (including air gaps) of given gap width (g) with circular apertures that narrow along the stack (FIG. **2***a*). An RF voltage of some frequency (w) and peak amplitude (U) applied to adjacent electrodes with opposite phases produces an oscillatory electric field near the funnel avails. The peak field intensity (A) rapidly drops when distancing from the walls, and the resulting Dehmelt potential repels ions toward the funnel axis, preventing their loss on the electrodes. A ladder of DC voltages is typically co-applied to electrodes to establish a potential gradient along the axis, which pulls confined ions through the funnel while compressing them to the diameter of the smallest exit aperture (d). In practice, the RF voltage is loaded onto the electrodes using two capacitor chains, one connected to the even-numbered electrodes and the other to the odd-numbered electrodes, and DC voltages are produced using a resistor chain. A pressure drop behind the funnel produces the vacuum suction and thus axial gas flow that accelerates toward the exit (FIG. **2***a*). This gas flow aids the DC field to pull ions along the funnel, and, depending on the funnel length, conical angle, and other design and operational parameters, may suffice to pull a large fraction of ions through the funnel even with no DC field. If the apertures narrow enough in terms of the electrode spacing (s), the RF field also creates axial traps that capture ions and impede their motion through the funnel. This effect rapidly grows as d decreases below 2 s, limiting the minimum practical final beam diameter to ~1.5 s-2 s. The entrance opening is not physically restricted and should be large enough to collect most or all of